UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Addr ss: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/341,407	10/12/99	DELOVITCH T	087300-00040

HM12/1105

KAREN B DOW
TOWNSEND AND TOWNSEND AND CREW
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO CA 94111-3834

EXAMINER	
ROARK, J	
ART UNIT	**PAPER NUMBER**
1644	15

DATE MAILED: 11/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/341,407	DELOVITCH, TERRY L.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *7 and 10-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 8/20/01 (Paper No. 12), is acknowledged.
Claims 1-31 are pending.

Claims 7 and 10-31 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-6 and 8-9 *are under consideration in the instant application.*

2. In order to facilitate the prosecution of this application, Applicant is requested to cancel all non-elected embodiments from the claims.

3. Applicant's supplemental IDS, filed 9/25/01, as Paper No. 14, is acknowledged. It is noted that the IDS filed 9/25/01 contains the same information as the Communication filed 8/28/01 (Paper No. 13).

References already of record have been considered, but have been crossed of the 1449 in order to avoid duplicate citations.

4. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 8/20/01 (Paper No. 12).
The rejections of record can be found in the previous Office Action (Paper No. 10).

It is noted that New Grounds of Rejection are set forth herein.

5. Claim 9 is objected to for the following informalities: it appears that the phrase "wherein human" should read -- wherein the human --. Appropriate correction is required.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The previous rejection of claims 1-6 and 8-9 under 35 U.S.C. 112, first paragraph, as not reasonably providing enablement for a method of preventing development of autoimmune diabetes in humans (as set forth in Section #11 of Paper No. 10), has been withdrawn in view of Applicant's convincing arguments based upon the susceptibility parameters set forth in the specification at page 8, lines 30-35.

8. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing the development of autoimmune diabetes with an agonist antibody to CD28; does not reasonably provide enablement for a method of preventing the development of other autoimmune diseases (claims 1-6) or a method employing any "CD28 agonist" (claims 1-2). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments with respect to the rejection of record have been fully considered, but have not been found convincing for the reasons of record and as set forth below.

With respect to the rejection of record, Applicant argues that a method which results in the stimulation of a TH2 type of T cell response is broadly applicable to a number of autoimmune diseases, irrespective of the antigens involved. Applicant points to Saoudi et al. (Eur. J. Immunol. 1993, 23:3096-3103, IDS #4) and Ekerfelt et al. (Clin. Exp. Immunol. 2001; 123:112-118, IDS #2) for support for this statement and as evidence that a number of autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, and lupus erythematosus are associated with a reduced TH2 phenotype. Applicant also argues that Thompson (Cell 81:979-982 1995, IDS #AO, of record), cited by the Examiner as evidence of unpredictability in the art of treating autoimmune diseases by modulating the CD28/B7 pathway, is not valid in the instant case which is limited to agonists of CD28. Applicant points to Weintraub et al. (J. Immunol. 1997; 159:4117-4126, IDS #5) and Karandikar et al. (J. Immunol. 1998; 161:192-199, IDS #3) for differences in the expression patterns of B7-2 and CD28.

While acknowledging that CD28 and its binding partners B7-1 and B7-2 are expressed on different cell types and that expression levels of the B7s vary as an immune response progresses; it is nevertheless submitted that blocking B7-1 or B7-2 alters signaling via their CD28 counter-receptor. Blocking both B7-1 and B7-2 would in effect antagonize CD28 signaling since neither B7 molecule would be available to bind CD28 and consequently no signal via CD28 would be generated. Differences in outcome between anti-B7-2 treatment in diabetes versus EAE minimally speak to the complexity of the system in various autoimmune disease, as recognized by the skilled artisan at the time of the invention and reviewed in Thompson. Inconsistent results by blocking B7-2 in different autoimmune diseases further emphasizes the system complexity and the variability between the different autoimmune diseases, even in autoimmune diseases considered to be "TH1" type diseases.

Further, not all autoimmune diseases would be viewed by the skilled artisan as likely to benefit from stimulating a TH2 type of immune response. Many autoimmune diseases, particularly systemic autoimmune diseases such as lupus, are generally considered to be the *result* of a TH2 type of response. In such autoimmune diseases the skilled artisan would expect that antagonists, rather than agonists, of signaling via CD28 would be more beneficial. Consistent with this, Liang et al. (J. Immunol. 1999; 163:2322-2329) teach that amelioration of lupus is brought about by treatments that block both B7 molecules (see entire document, especially Discussion on page 2328). Blocking both B7 molecules would be expected to antagonize CD28 signaling since neither B7-2 nor B7-1 would be available to stimulate CD28 on T cells. However, even in view of beneficial results obtained by antagonizing the CD28/B7 pathway in a mouse model of lupus; Liang et al. still conclude that the role of costimulation in the pathogenesis of lupus is complex, and that a greater understanding would be required to fully appreciate the potential therapeutic benefits of manipulating costimulatory pathways (see especially concluding remarks on page 2328).

In addition, while several autoimmune diseases can be broadly characterized as "TH1 type" based upon cytokine profiles and cellular immunity (such as the experimental allergic neuritis model of Ekerfelt et al. and the autoimmune uveoretinitis model of Saoudi et al. cited by Applicant); these disease are nevertheless diverse. As noted previously, the skilled artisan recognized that different antigens are involved in the different diseases, which means the timing of the antigen exposure likely differs for each antigen and therefore the timing for interventional therapy also differs. The TH1 diseases discussed by Saoudi et al. and Ekerfelt et al. are experimentally induced so the timing of antigen stimulation is known, thus intervention at a particular point in the development of the immune response is possible. This is not usually the case in human autoimmune diseases which arise spontaneously. The pathophysiology and natural history of different autoimmune diseases is distinct. Thus the ability to identify susceptible individuals varies greatly for each disease and depends upon disease-specific criteria; consequently the ability to intervene at a particular point in the development of the immune response varies greatly.

Thus the skilled artisan clearly recognized the complexities both of the CD28/B7 costimulatory pathway, and of manipulating different autoimmune diseases. Applicant does not appear to have provided sufficient guidance as to how to apply CD28 agonist therapy to autoimmune diseases commensurate in scope with the claims. Methods of preventing the development of different autoimmune diseases requires guidance with respect to that particular disease because each disease is a complex and unique immune response having different stimuli and courses of development.

In addition, although the specification provides a working example of an agonist CD28 antibody, and provides guidance as to how to identify forms of a B7-2 protein with CD28 agonist activity for use in the instant method (e.g. specification at page 7, lines 19-34), there does not appear to be sufficient guidance with respect to how to make and use other "CD28 agonists" commensurate in scope with the instant claims. While "CD28 agonist" may have some notion of a desired activity; there is insufficient biochemical or structural information to enable the skilled artisan to make and use the "CD28 agonist", as broadly claimed. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992). The skilled artisan was aware that producing CD28 agonists other than antibodies and agonist forms of known CD28 co-receptors was highly unpredictable. For example, Instant claims 1 and 2 as currently recited still encompass any molecule that is a "CD28 agonist", thus for these claims, as currently recited, enablement does not appear to be commensurate with the scope of the claims.

In view of the complex nature of the CD28/B7 pathway and the lack of predictability associated with manipulating this pathway in autoimmune diseases other than diabetes and with CD28 agonists other than CD28 agonist antibodies or CD28 agonist forms of B7-2; the absence of working examples addressing autoimmune diseases other than diabetes or CD28 agonists other than a CD28 agonist antibody; and the lack of guidance with respect to diseases other than diabetes or other CD28 agonists; the skilled artisan would not be able to practice the invention commensurate in scope with the claims, without undue experimentation.

9. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite "CD28 agonist" as an essential feature of the invention.

The Examiner notes that the claimed invention may be adequately described if there is a (1) sufficient description of a *representative number of species*, or (2) by disclosure of *relevant, identifying characteristics* sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. See the Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

However, while agonists comprising antibodies to CD28 and forms of B7-2 proteins having CD28 agonist activity appear to have adequate written support in the specification as filed; these two species are structurally diverse. "CD28 agonist" is a broad genus encompassing any molecule with that activity. However, only two species with this activity appear to be disclosed and this is insufficient to support a genus encompassing structurally diverse molecules ranging from antibodies to peptidomimetics to inorganic compounds. Nor does Applicant appear to identify a relevant identifying characteristic that would permit the skilled artisan to recognize which molecules were included in the genus. Thus there is insufficient written description in the specification as-filed of a "CD28 agonist" as recited in the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over
Rabinovitch (Diabetes 43:613-621 1994, IDS-AH)
and Lenschow et al. (Immunity 5:285-293 Sept. 1996, IDS-Y),
in view of *either*
King et al. (Eur. J. Immunol. 25:587-595 1995, IDS-W), *or*
Webb et al. (Blood 86:3479-3486 1995, IDS-AQ).

Applicant's argument's, filed 8/20/01, have been fully considered but have not been found convincing, essentially for the reasons of record. In view of the withdrawal of the previous rejection under 35 USC 112, first paragraph; claims 5-6 and 8-9 have now been considered with respect to the prior art. These issues are addressed in the context of a reiteration of the rejection of record.

The claims are drawn to a method of preventing diabetes by administering a monoclonal antibody that is a CD28 agonist.

Rabinovitch teaches that multiple immunostimulatory procedures prevent IDDM (autoimmune diabetes) in the NOD mouse (see entire document, e.g., "Title"). Rabinovitch also teaches that the immunostimulation protects from diabetes by favoring T cell differentiation along a protective TH2 pathway, thus downregulating the destructive TH1 response (e.g. page 616-619 "Immunostimulatory Procedures Prevent IDDM: Correction of a Cytokine Balance?", especially page 618-619 bridging paragraph). Rabinovitch concludes that the findings in the NOD mouse provide a basis for considering immunostimulation in attempts to prevent IDDM (autoimmune diabetes) in humans at risk for this disease (e.g., concluding paragraph page 619).

Lenschow et al. teach that the absence of signaling through CD28 in the NOD mouse leads to an accelerated development of diabetes due to the development of a dominant TH1 response (e.g., "Discussion" page 290, especially end of 1st full paragraph). Lenschow et al. further teach that the increased incidence of diabetes occurs when signaling through CD28 is blocked during the first two weeks of life (e.g., page 290, 2nd column, bottom ¼ of text).

Neither Rabinovitch nor Lenschow et al. teach preventing development of diabetes by administering an agonistic anti-CD28 antibody.

Although Applicant has argued that Lenschow et al. do not teach that ligation of the CD28 receptor in the NOD mouse would lead to an opposite effect (i.e., protection rather than acceleration of development of diabetes), it is noted that specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). In re Burckel is cited in MPEP 716.02. Further, Lenschow et al. conclude that it is a disruption of CD28 *signaling* from birth that exacerbates diabetes (e.g., page 289, last full sentence of 1st column). Lenschow et al. also note that disruption of CD28 signaling resulted in a decreased ability to mount a TH2 response (e.g., page 290 1st full paragraph). Throughout the Discussion on pages 290-291, Lenschow et al. clearly teach that it is the inhibition of CD28 signaling during the first two weeks of life that exacerbates disease, thus this teaching would suggest to one of ordinary skill in the art at the time the invention was made that the opposite method of stimulating CD28 signaling during this critical window would have the opposite effect of inducing a TH2 response and protecting from development of diabetes. Obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). MPEP 2143.02.

Both King et al. and Webb et al. teach that a CD28 agonist monoclonal antibody induces a TH2 response (see entire document of each, especially "Abstract" and "Methods").

Applicant argues that the *in vitro* studies of King et al. and Webb et al. does not provide a reasonable expectation that similar results would be obtained *in vivo*. However, it is again noted that obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). MPEP 2143.02. Further, Applicant's arguments do not provide objective evidence that these agonistic anti-CD28 antibodies would not have the same effect on T helper cell differentiation to TH2 cells *in vivo* as *in vitro*.

Given the teachings of the references, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize an agonistic anti-CD28 antibody in a method for preventing the development of autoimmune diabetes. The ordinary artisan at the time the invention was made would have been motivated to administer an agonistic anti-CD28 antibody such as those taught by King et al. or Webb et al. with the expectation of stimulating the development of a TH2 response and thus preventing the development of diabetes, as taught by both Rabinovitch and Lenschow et al. The teachings of both King et al. and Webb et al. show that the ordinary artisan at the time the invention was made would have recognized that an antibody could be used to stimulate CD28, and further that this stimulation results in the TH2 type of response that both Rabinovitch and Lenschow et al. teach protects susceptible subjects, including human subjects, from diabetes. Consequently, the teachings of the references also indicate that the ordinary artisan would have had a reasonable expectation of success in preventing development of diabetes, including in humans. In view of the teachings of Lenschow et al. that the critical window is in the first two weeks of life in the murine model, the ordinary artisan would have been further motivated to select human subjects for therapy in the corresponding period of life, i.e., at from about 6 months to about 2-3 years. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
November 2, 2001

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
11/2/01